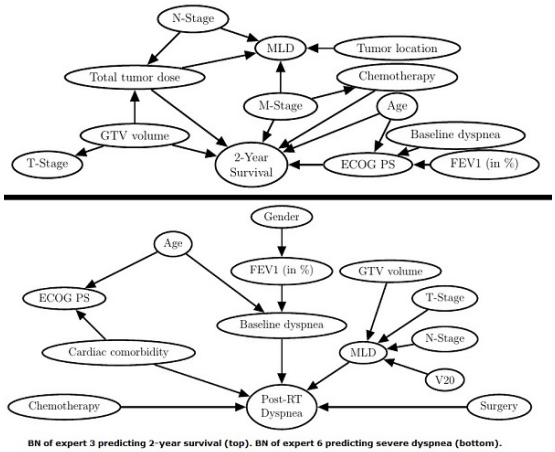
Results: Expert networks were more complex with up to 30 arcs while the data-driven algorithm selected no more than 6 arcs. Expert and data-driven models were not significantly different in discriminative ability (see 95% confidence intervals in table). Further, AUCs of all models except expert 6 were not significantly different from 0.5. Patients with 2-year survival could be discriminated better as it was significantly different from chance in 4 expert models and the data-driven model. The data-driven model was significantly better than two expert models.
Conclusions: Discrimination of patients with 2-year survival after lung RT is achievable with both methodologies – expert-based and data-driven models. Reliable discrimination of patients with severe dyspnea after RT is not achievable with the presented models learned on data of 792 patients. Neither expert-based or data-driven models outperform each other. Thus, there is dire need for biomarkers predictive of radiation-induced dyspnea. For both endpoints, the algorithmically derived models are more parsimonious and perform as well as the expert-based models or better.

		Predicting Severe Dyspnea (CTCAE dyspnea scores ≥2)				2-Year Survival			
		AUC	AUC 95%CI	(AUC - AUC$_{Alg.}$) 95% CI	# Arcs	AUC	AUC 95%CI	(AUC - AUC$_{Alg.}$) 95% CI	# Arcs
Expert	1	0.58	[0.42,0.73]	[-0.07,0.22]	30	0.59	[0.48,0.7]	[-0.27,0.01]	19
	2	0.61	[0.43,0.77]	[-0.14,0.32]	9	0.65	[0.54,0.76]	[-0.21,0.07]	15
	3	0.49	[0.32,0.65]	[-0.19,0.15]	23	0.69	[0.58,0.8]	[-0.13,0.1]	17
	4	0.59	[0.45,0.73]	[-0.06,0.22]	22	0.56	[0.44,0.68]	[-0.32,-0.01]	23
	5	0.65	[0.5,0.8]	[-0.05,0.32]	20	0.53	[0.4,0.65]	[-0.36,-0.01]	13
	6	0.69	[0.56,0.83]	[-0.03,0.39]	14	0.64	[0.53,0.75]	[-0.21,0.05]	16
	7	0.57	[0.43,0.7]	[-0.08,0.2]	7	0.68	[0.57,0.79]	[-0.19,0.12]	20
Alg.		0.52	[0.38,0.66]	[0,0]	6	0.72	[0.6,0.82]	[0,0]	4



BN of expert 3 predicting 2-year survival (top). BN of expert 6 predicting severe dyspnea (bottom).

Keywords: personalized radiotherapy, Bayesian prediction modelling

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Proton Radiation Therapy: Current Status at Massachusetts General Hospital
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Purpose: Because of the absence of exit dose beyond the Bragg peak, protons can improve the radiotherapy physical dose distribution. This offers the potential for dose escalation to improve local control in anatomic sites and histologies where local control of tumor is suboptimal with photons. At the same time, the reduction in the normal tissue dose/volume profile is anticipated to reduce acute and late normal tissue toxicity. The competing technologies include intensity modulated photon radiation therapy (IMRT) as well as heavier charged particles. Massachusetts General Hospital (MGH) has been a pioneer in the development of proton radiation therapy. An overview of the proton radiation therapy program at MGH will be provided which will illustrate technological progress in proton therapy.
Materials/Methods: The initial treatment facility was in the Harvard Cyclotron Laboratory, a physics laboratory which was modified to accommodate patient treatments. Beam generated in a 160 MeV cyclotron was delivered via fixed horizontal beams. In 2001, the program was moved to a dedicated clinical facility based at the hospital, the Francis H. Burr Proton Therapy Center (FHBPTC). In 2017, an additional single room, gantry-based treatment facility will open.
Results: The FHBPTC has a 230 MeV cyclotron delivering beam to two rooms equipped with 360-degree rotational gantries and a third clinical room with a two beam-lines, one dedicated for treatment of eye tumors and the other for stereotactic intracranial radiosurgery/radiotherapy. In 2014, we delivered 13, 370 patient treatments at the FHBPTC. Currently, one of the two gantries delivers scanned proton beams including intensity modulated proton therapy. The other gantry delivers passively scattered proton treatments. We have U.S. National Cancer Institute funding to support clinical trials of intensity modulated proton therapy and to study the clinical impact of differences between proton and photon dose distributions, to optimize IMPT delivery including robust optimization, and to study proton dose perturbations caused by the heterogeneous patient and inter- and intra-factional variations. We are also active participants in ongoing NRG Oncology proton clinical trials.
Conclusions: Proton radiation therapy offers a number of potential treatment advantages to patients over photons related primarily to differences in physical dose distribution; clinical gain can be assessed in clinical trials which are currently in progress. Rapid changes in technology must be considered in designing and conducting clinical trials in this area.

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Macrophage reprogramming for anticancer therapy
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Tumor-associated macrophages (TAMs) are a phenotypically and functionally heterogeneous assortment of monocyte-derived cells that participate to key processes associated with tumor progression, such as angiogenesis, immunosuppression, invasion, and metastasis. Increasing studies also show that TAMs can either enhance or antagonize the antitumor efficacy of cytotoxic chemotherapy, cancer-cell targeting antibodies, and immunotherapeutic agents, depending on the tumor type, macrophage activation state, or type of treatment. TAMs can also drive reparative mechanisms in tumors after radiotherapy or treatment with antiangiogenic drugs. At the meeting, I will discuss the biological significance and clinical implications of these findings, with an emphasis on novel approaches, based on microRNA (miRNA) targeting, to reprogram TAMs into immunostimulatory cells. Indeed, we found that efficient miRNA depletion in TAMs did not alter their abundance in the tumors, but markedly reprogrammed their transcriptomes and effector functions from immunosuppressive to immunostimulatory. This enhanced cytotoxic T-cell infiltration, abated tumor progression, and increased tumor responsiveness to immune checkpoint blockade. Bioinformatics analysis of TAM transcriptomes identified a limited set of miRNAs putatively involved in TAM programming, and re-expression of Let-7 in Dicer-deficient TAMs was sufficient to rescue TAM's protumoral phenotype and abate tumor CTL infiltration. Collectively, these results have identified a mechanism of TAM programming to an immunostimulatory phenotype that may be exploited to enhance the efficacy of cancer immunotherapies.

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The search for genetic predictors of radiotherapy response